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InheriGene

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Patient Details

Sample ID	XXX	**Sample Collection Date**	--/--/--
Sample Receiving Date	--/--/--	**Sample Reporting Date**	--/--/--
Patient Name	XXX	**Patient Location**	XXX
Age	XX	**Gender**	M/F

Clinical Indications

DISEASE HISTORY			
PROBAND	**PARENTAL**		**SIBLING**
SELF	**FATHER**	**MOTHER**	
• **Neonatal Onset Epileptic Encephalopathy**	-	-	

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Pathogenic variant detected related to the clinical phenotypes

Results:

Main Findings

Gene (Exon) [Transcript]	Variant (Amino acid Alteration)	Variant (Coding)	Inheritance	Zygosity	Disease	Interpretation
POLG (exon19) [NM_002693.3]	p.Q1023X	c.C3067T	Autosomal Dominant	Heterozygous	Progressive External Ophthalmoplegia (OMIM:157640)	Pathogenic

- Genetic test results are reported based on the recommendations of American College of Medical Genetics.
- There are Five-Tiered Classification based on ACMG guidelines [PMID: 25741868] i.e. Pathogenic, Likely Pathogenic, Variant of Unknown Significance (VUS), Likely Benign, Benign
- No other variant that warrants to be reported was detected. Variations with high minor allele frequencies which are likely to be benign will be given upon request.
- Data revaluation performed upon the upgradation of databases used and results may vary in accordance.

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Incidental Findings*

Gene (Exon) [Transcript]	Variant (Amino acid Alteration)	Variant (Coding)	Inheritance	Zygosity	Disease	Interpretation
GJB2 (exon2) [NM_004004.6]	p.W24X	c.G71A	Digenic Dominant, Autosomal Recessive	Heterozygous	Deafness (OMIM:220290)	Pathogenic

*The incidental findings reported here are not based on the clinical phenotype of the individual.

- These findings are identified as part of the genomic analysis and may not directly correlate with the individual's current health condition or symptoms.
- If additional information or clarification is required regarding these findings, it will be provided upon request.

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Variant Interpretation

POLG; c.C3067T; p.Q1023X	
GENOMIC LOCATION	chr15:89319265
VARIANT TYPE	Frameshift
VARIANT ALLELE DEPTH	45
TOTAL ALLELE DEPTH	89
POPULATION FREQUENCY	gnomAD: 0.00001; ExAC: 0.000021
ASSOCIATED DISEASE	Progressive External Ophthalmoplegia (OMIM:157640)
PREDICTION ALGORITHMS	SIFT: D; POLYPHEN: D; MUTATIONTASTER: A *D=DELETERIOUS/DAMAGING/DISEASE_CAUSING; T=TOLERATED; P=POSSIBLY DAMAGING; B: BENIGN; A: DISEASE-CAUSING AUTOMATIC; N: POLYMORPHISM; P: POLYMORPHISM_AUTOMATIC . = NO INFORMATION FOUND

Disease Summary

Progressive External Ophthalmoplegia

- Chronic Progressive External Ophthalmoplegia (CPEO) is a condition characterized mainly by a loss of the muscle functions involved in eye and eyelid movement. Signs and symptoms tend to begin in early adulthood and most commonly include weakness or paralysis of the muscles that move the eye (ophthalmoplegia) and drooping of the eyelids (ptosis). Some affected individuals also have general weakness of the skeletal muscles (myopathy), which may be especially noticeable during exercise. Muscle weakness may also cause difficulty swallowing (dysphagia). CPEO can be caused by genetic changes in any of several genes, which may be located in mitochondrial DNA or nuclear DNA. It has different inheritance patterns depending on the gene involved in the affected individual. CPEO can occur as part of other underlying conditions, such as ataxia neuropathy spectrum and Kearns-Sayre syndrome. These conditions may not only involve CPEO, but various additional features that are not shared by most individuals with CPEO.[GARD:4503]

- Chronic ophthalmoplegia is characterised by progressive weakness of ocular muscles and levator muscle of the upper eyelid. The condition is mainly manifested in adults. It may be totally and permanently isolated, however in a minority of cases it is associated with skeletal myopathy, which causes abnormal fatigability and even permanent muscle weakness. In this case the affection is still termed isolated progressive external ophthalmoplegia. A large proportion of chronic ophthalmoplegias presents with multisystemic pattern of signs: neurological signs (hearing loss, retinopathy, cerebellar disorders, peripheral neuropathy, etc.), endocrine (diabetes, hypogonadism, hypoparathyroidism, etc.), kidney (kidney failure, tubulopathy, etc.), and heart disorders (conduction disorders, myocardiopathy, etc.).[ICD-11:9C82.0]

Gene Summary

POLG

- Mitochondrial DNA polymerase is heterotrimeric, consisting of a homodimer of accessory subunits plus a catalytic subunit. The protein encoded by this gene is the catalytic subunit of mitochondrial DNA polymerase. The encoded protein contains a polyglutamine tract near its N-terminus that may be polymorphic. Defects in this gene are a cause of Progressive External Ophthalmoplegia With Mitochondrial DNA Deletions 1 (PEOA1), Sensory Ataxic Neuropathy Dysarthria And Ophthalmoparesis (SANDO), Alpers-Huttenlocher Syndrome (AHS), and Mitochondrial Neurogastrointestinal Encephalopathy Syndrome (MNGIE). Two transcript variants encoding the same protein have been found for this gene. [provided by RefSeq, Jul 2008]

Recommendations:

1. Genetic counseling is advised to interpret the potential consequences of the variant(s).
2. If results do not align with the clinical findings, additional testing should be considered based on the referring clinician's recommendation.
3. For confirmation of pathogenic variants, perform Sanger sequencing of the targeted region identified through preliminary screening, ensuring bidirectional sequencing for accuracy.

Methodology:

1. Sample Collection and Extraction, Library Preparation, and Sequencing was done by Partnered Lab.
2. Data Analysis:
   We use a customized algorithm developed at Genomiki Solutions for data analysis. The algorithm integrates quality control, read alignment to the human reference genome (GRCh38) using BWA, and variant identification tailored to enhance accuracy and efficiency for genomic data interpretation.
3. Clinical Annotation:
   Variants are annotated based on their clinical relevance using data from published literature and in-house curated databases. These curated databases provide key information, including minor allele frequency, to enhance the accuracy and depth of the annotation process.

Limitations:

1. Genetic testing may not always provide definitive answers due to evolving medical knowledge and technology.
2. Accurate interpretation relies on comprehensive clinical and family history. Misinterpretation may arise if such information is incomplete.
3. Variations in coding regions that cannot be sequenced due to technological constraints may not be identified.
4. Mosaicism, rare technical errors or recent transfusions may impact result accuracy.
5. The results are based on the available medical knowledge at the time of analysis; if new evidence arises, reanalysis can be requested.

Disclaimer:

1. Data Accuracy: The interpretations are based on the quality of the input data. Inaccurate or degraded sample quality may impact results.
2. Variant Classification: Variants classified as "Uncertain Significance" should not be used as the sole basis for clinical decisions. Further research or testing may be necessary.
3. Updates to Guidelines: As scientific understanding evolves; variant classifications and interpretations may change. Regular updates to clinical reports may be necessary.
4. Inheritance Patterns: This report does not account for inheritance patterns unless explicitly analyzed and reported.
5. Third-party Testing: Results from this report should not be compared with those from other laboratories without proper reconciliation of methodologies.
6. Scope of Testing: This test analyzes only the regions of interest specified. Variants outside the tested regions are not detected and cannot be interpreted.
7. Secondary Findings: This test does not analyze or report on unrelated secondary findings unless explicitly included in the test scope.
8. Laboratory Standards: All analyses are performed by current quality control and quality assurance standards relevant to the laboratory's accreditation.
9. Use of Computational Tools: Computational predictions provided (if any) are adjunctive to clinical judgment and are not definitive.
10. Counselling Recommendation: Patients are strongly encouraged to seek genetic counselling to understand the results and implications.
11. Non-diagnostic Nature: This test does not comprehensively assess all genetic disorders or conditions.
12. Data Sharing: Results and anonymized data may be used for quality control or research purposes, adhering to applicable data privacy regulations.

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